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12-31-98 R2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

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Serial No: 08/862,192

Filed: 05/23/97

For: Prediction of Relative Binding Motifs of Biologically Active Peptides and Peptide Mimetics

GROUP ART UNIT: 2762

EXAMINER: Davis, G.

AMENDMENT

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

In response to the Office Action dated 6/23/98 in connection with the above-identified application, please enter and consider the amendments and remarks set forth below.

Date of Deposit 12/16/98

I hereby certify under 37 CFR 1.8(a) that this correspondence is being deposited with the United States Postal Service as **first class mail** with sufficient postage on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D C 20231.

NANCY GRANT

Nancy Grant

IN THE SPECIFICATION:

On p. 2, l. 16, delete "is required".

On p. 6, l. 23, replace the blank with "the Division of Biological Sciences for the University of Missouri".

IN THE CLAIMS:

1. (Amended) A computer-implemented method for identifying relative binding motifs of peptide-like molecules, comprising the steps of:

(a) training [an] a computer-implemented artificial neural network (ANN) with input data characterizing a set of training peptide-like molecules, each of known sequence and binding affinity;

(b) applying to the ANN input data characterizing at least one test peptide-like molecule, each of known sequence but unknown binding affinity;

(c) analyzing each applied test peptide-like molecule using the ANN to [predict] generate a prediction of a relative binding affinity for each test peptide-like molecule, and outputting such prediction.

(Amended) A computer-implemented method for identifying relative peptide binding motifs, comprising the steps of:

(a) training [an] a computer-implemented artificial neural network (ANN) with input data characterizing a set of training peptides, each of known binding affinity, each peptide comprising a sequence of amino acids, each amino acid being binary coded as having or lacking specific features generally characteristic of amino acids;

(b) applying to the ANN input data characterizing at least one test peptide, each of unknown binding affinity, each peptide comprising a sequence of amino acids, each amino acid being binary coded as having or lacking specific features generally characteristic of amino acids;

(c) analyzing each applied test peptide using the ANN to [predict] generate a prediction of a relative binding affinity for each test peptide, and outputting such prediction.

(Amended) The method of claim 2, wherein the set of training peptides include peptides having a binding affinity for [MHC] major histocompatiblity complex (MHC) class I molecules.

(*Reiterated*) The method of claim 3, wherein the peptides included in the set of training peptides have a binding affinity for mouse MHC class I K^b.

(*Reiterated*) The method of claim 2, wherein the set of test peptides include peptides having a binding affinity for MHC class I molecules.

(*Reiterated*) The method of claim 5, wherein the peptides included in the set of test peptides have a binding affinity for mouse MHC class I K^b.

(*Reiterated*) The method of claims 1 or 2, wherein the ANN comprises a multi-layer perceptron ANN trained by back-propagation of error.

8. A computer-implemented system for identifying relative binding motifs for peptide-like molecules, comprising:

(a) means for training [an] a computer-implemented artificial neural network (ANN) with input data characterizing a set of training peptide-like molecules, each of known sequence and binding affinity;

(b) means for applying to the ANN input data characterizing at least one test peptide-like molecule, each of known sequence but unknown binding affinity;

(c) means for analyzing each applied test peptide-like molecule using the ANN to [predict] generate a prediction of a relative binding affinity for each test peptide-like molecule, and output such prediction.

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A computer-implemented system for identifying relative peptide binding motifs, comprising:

(a) means for training [an] a computer-implemented artificial neural network (ANN) with input data characterizing a set of training peptides, each of known binding affinity, each peptide comprising a sequence of amino acids, each amino acid being binary coded as having or lacking specific features generally characteristic of amino acids;

(b) means for applying to the ANN input data characterizing at least one test peptide, each of unknown binding affinity, each peptide comprising a sequence of amino acids, each amino acid being binary coded as having or lacking specific features generally characteristic of amino acids;

(c) means for analyzing each applied test peptide using the ANN to [predict] generate a prediction of a relative binding affinity for each test peptide, and output such prediction.

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(Amended) The system of claim 9, wherein the set of training peptides include peptides having a binding affinity for [MHC] major histocompatiblity complex (MHC) class I molecules.

(*Reiterated*) The system of claim 10, wherein the peptides included in the set of training peptides have a binding affinity for mouse MHC class I K^b.

(*Reiterated*) The system of claim 9, wherein the set of test peptides include peptides having a binding affinity for MHC class I molecules.

(*Reiterated*) The system of claim 12, wherein the peptides included in the set of test peptides have a binding affinity for mouse MHC class I K^b.

(*Reiterated*) The system of claims 8 or 9, wherein the ANN comprises a multi-layer perceptron ANN trained by back-propagation of error.

15. (Amended) A computer program, residing on a computer-readable medium, for identifying relative binding motifs for peptide-like molecules, comprising instructions for causing a computer to:

(a) train [an] a computer-implemented artificial neural network (ANN) with input data characterizing a set of training peptide-like molecules, each of known sequence and binding affinity;

(b) apply to the ANN input data characterizing at least one test peptide-like molecule, each of known sequence but unknown binding affinity;

(c) analyze each applied test peptide-like molecule using the ANN to [predict] generate a prediction of a relative binding affinity for each test peptide-like molecule, and output such prediction.

(Amended) A computer program, residing on a computer-readable medium, for identifying relative peptide binding motifs, comprising instructions for causing a computer to:

(a) train [an] a computer-implemented artificial neural network (ANN) with input data characterizing a set of training peptides, each of known binding affinity, each peptide comprising a sequence of amino acids, each amino acid being binary coded as having or lacking specific features generally characteristic of amino acids;

(b) apply to the ANN input data characterizing at least one test peptide, each of unknown binding affinity, each peptide comprising a sequence of amino acids, each amino acid being binary coded as having or lacking specific features generally characteristic of amino acids;

(c) analyze each applied test peptide using the ANN to [predict] generate a prediction of a relative binding affinity for each test peptide, and output such prediction.

17. (Amended) The computer program of claim 16, wherein the set of training peptides having a binding affinity for [MHC] major histocompatiblity complex (MHC) class I molecules.

18. (*Reiterated*) The computer program of claim 17, wherein the peptides included in the set of training peptides have a binding affinity for mouse MHC class I K^b.

19. (*Reiterated*) The computer program of claim 16, wherein the set of test peptides include peptides having a binding affinity for MHC class I molecules.

20. (*Reiterated*) The computer program of claim 19, wherein the peptides included in the set of test peptides have a binding affinity for mouse MHC class I K^b.

21. (*Reiterated*) The computer program of claims 15 or 16, wherein the ANN comprises a multi-layer perceptron ANN trained by back-propagation of error.

REMARKS

Claims 1-21 were in issue. By this amendment, claims 1-3, 8-10, and 15-17 have been amended, no claims have been canceled, and no claims have been added. Accordingly, claims 1-21 are presented and at issue. No new matter has been added.

The §101 Rejection

The Examiner has rejected claims 1-6, 8-13, and 15-20 under 35 U.S.C. §101 as covering non-statutory subject matter. Applicant respectfully traverses this rejection with respect to the claims as amended.

The Examiner's analysis of these claims is not in accordance with present law. First, the treatment of "means plus function" claims" in the present context has been defined by the Federal Circuit as follows:

> "This court, in banc, has determined that claims written in means-plus-function format contain statutory subject matter *even if functional phrases of the means limitations recite mathematical calculations*. See *Alappat*, 33 F.3d at 1544, 31 U.S.P.Q.2D (BNA) at 1558. Therefore, the claims of the [patent in issue] do not wholly preempt the use of mathematical calculations because the claims are limited to the structure disclosed in the specification and equivalent structures for performing the claimed functions." *Schlafly v. Caro-Kann Corporation*, 1998 U.S. App. LEXIS 8250; 1998-1 Trade Cas. (CCH) P72,138; 40 Fed. R. Serv. 3d (Callaghan) 790 (Fed. Cir. 1998) (emphasis added).

In the present case, embodiments for implementing the invention are described as a neural network (shown in FIG. 1 and described on pp. 5-6), appropriate programming, and implementation in either hardware or software (see p. 14).

Second, the test for patentable subject matter was recently clarified by the Federal Circuit:

> "Today, we hold that the transformation of data ... by a machine through a series of mathematical calculations into a final [output] constitutes a practical application of a mathematical algorithm, formula, or calculation, because it produces "a useful, concrete and tangible result" ...." *State Street Bank & Trust Co. v. Signature Financial Group, Inc.*, __ F.3d __ (Fed. Cir. 1998).

In *State Street*, the "useful, concrete and tangible result" was a final share price, calculated from transformation of data representing discrete dollar amounts.

While the claims as originally presented (particularly the "Beauregard" style claims 15-21, which are directed to a computer program) met the criteria for statutory subject matter, Applicant has clarified these claims to explicitly recite the use of a computer. Hence, the claims cover training a computer-implemented artificial neural network (ANN), applying the ANN to input data characterizing at least one test peptide-like molecule, and analyzing each applied test peptide-like molecule using the ANN to generate a prediction of a relative binding affinity for each test peptide-like molecule, and output such prediction. The output constitutes a "useful, concrete and tangible result" – information about the test molecule not previously known.

The §102 Rejection

The Examiner has rejected claims 1-21 under 35 U.S.C. §102(b) as being anticipated by each of the references to Metfessel, Riis, Holley and Kneller. Applicant respectfully traverses this rejection with respect to the claims as amended.

The independent claims as amended require *generation of a prediction of a relative binding affinity*. For example, claim 1 requires "analyzing each applied test peptide-like molecule using the ANN *to generate a prediction of a relative binding affinity* for each test peptide-like molecule, and outputting such prediction." The cited art does not teach at least this element. For Class I major histocompatibility complex (MHC) molecules, the affinity of the bound peptides largely determines the stability of the expressed class I molecules and their recognition by immuno-surveillant cytotoxic T-cells. To the best of Applicants' knowledge, artificial neural network analysis has not been successfully applied to prediction of binding affinities of biologically active peptides and peptide mimetics.

All 4 cited references teach using various statistical analyses and neural networks to predict protein *structure* (not binding affinity) from the primary, secondary, and some tertiary *structural* characteristics of a *protein* sequence. Such sequences are typically much longer than peptides (*e.g.*, peptides eluted from class I MHC molecules reveal that they are short, usually 8-10 amino acids long). Applicants' reading of these 4 references does not find any mention of predicting binding

affinity. Moreover, prediction of structure does not inherently provide information regarding binding affinity. For example, it is well known that a conservative amino acid change in an amino acid sequence can provide for a similar tertiary structure but a different binding affinity. Accordingly, these references lack an element claimed by Applicants, and thus fails as a §102 reference.

Accordingly, Applicant submits that none of the references, alone or in combination, anticipate or make obvious the invention as presently claimed. Applicant submits that this case is now in condition for allowance. Therefore, Applicant respectfully requests reconsideration and reexamination of the present application and allowance of the case at an early date.

Please apply any credits or charge any deficiencies to our Deposit Account No. 06-1050.

Respectfully submitted,

FISH & RICHARDSON

Dated: December 15, 1998

By: John Land, Reg. No. 29,554

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